

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year)

03 October 1997 (03.10.97)

International application No.

PCT/CA97/00163

Applicant's or agent's file reference

1038-680 MIS/ms

International filing date (day/month/year)

07 March 1997 (07.03.97)

Priority date (day/month/year)

08 March 1996 (08.03.96)

Applicant

MYERS, Lisa, E. et al

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

18 September 1997 (18.09.97)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Aino Metcalfe

Telephone No.: (41-22) 338.83.38

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 1038-680 MIS/ms	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/CA 97/ 00163	International filing date (day/month/year) 07/03/1997	(Earliest) Priority Date (day/month/year) 08/03/1996
Applicant CONNAUGHT LABORATORIES LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ Certain claims were found unsearchable (see Box I).

2. ☐ Unity of invention is lacking (see Box II).

3. ☒ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing

☐ filed with the international application.

☒ furnished by the applicant separately from the international application,

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority

4. With regard to the title, ☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

Figure No. _____ ☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 23
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 23 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/22 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 97 13785 A (CONNAUGHT LAB ; YANG YAN PING (CA); MYERS LISA E (CA); HARKNESS ROB) 17 April 1997 see the whole document ---	1-25
Y	WO 90 12591 A (UNIV TECHNOLOGIES INTERNATIONA ; SCHRYVERS ANTHONY BERNARD (CA)) 1 November 1990 see claims 1-26 --- -/--	1-25



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

* & * document member of the same patent family

Date of the actual completion of the international search

17 July 1997

Date of mailing of the international search report

30.07.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

Nauche, S

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MICROBIAL PATHOGENESIS, vol. 15, 1993, pages 433-445, XP000612196 RAONG-HUA YU ET AL: "THE INTERACTION BETWEEN HUMAN TRANSFERRIN AND TRANSFERRIN BINDING PROTEIN 2 FROM MORAXELLA (BRANHAMELLA) CATARRHALIS DIFFERS FROM THAT OF OTHER HUMAN PATHOGENS" see the whole document ---	1-25
A	WO 95 33049 A (PASTEUR MERIEUX SERUMS VACC ;TRANSGENE SA (FR); MILLET MARIE JOSE) 7 December 1995 see the whole document ---	1-25
A	WO 93 08283 A (UNIV SASKATCHEWAN) 29 April 1993 see the whole document -----	1-25

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 97/00163

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9713785 A	17-04-97	AU 7208296 A	30-04-97
WO 9012591 A	01-11-90	US 5292869 A	08-03-94
		AU 649950 B	09-06-94
		AU 5526190 A	16-11-90
		EP 0528787 A	03-03-93
		JP 4506794 T	26-11-92
		NZ 247967 A	24-02-95
		US 5141743 A	25-08-92
WO 9533049 A	07-12-95	FR 2720408 A	01-12-95
		AU 2675795 A	21-12-95
		CA 2167936 A	07-12-95
		EP 0720653 A	10-07-96
		FI 960428 A	28-03-96
		HU 75992 A	28-05-97
		JP 9501059 T	04-02-97
		NO 960332 A	21-03-96
WO 9308283 A	29-04-93	US 5417971 A	23-05-95
		AU 2751392 A	21-05-93
		CA 2121364 A	29-04-93
		EP 0610260 A	17-08-94
		US 5521072 A	28-05-96

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1038-680 MIS/ms	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)	
International application No. PCT/CA97/00163	International filing date (day/month/year) 07/03/1997	Priority date (day/month/year) 08/03/1996
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant CONNAUGHT LABORATORIES LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 6 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 18/09/1997	Date of completion of this report 19.06.98
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Pilat, D Telephone No. (+49-89) 2399-8668 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA97/00163

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-62 as originally filed

Claims, No.:

1-25 as originally filed

Drawings, sheets:

1/84-84/84 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 23.

because:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA97/00163

- ☒ the said international application, or the said claims Nos. 23 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17,19-25
	No:	Claims	18
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17,19-25
Industrial applicability (IA)	Yes:	Claims	1-22,24-25
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1) Reference is made to the following documents:

D1 Microbial Pathogenesis vol.15, 1993, p.433-445 Raong-Hua Yu et al.
D2 WO-A-9012591

1.1) The priority documents pertaining to the present application were not available at the time of establishing this written opinion. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If this is not correct, the E document cited in the international search report may become relevant to assess whether claims 1-25 satisfy the criteria set forth in Article 33(1) PCT.

2) Novelty (Article 33 (2) PCT)

2.1 The proteins Tbp1 and Tbp2 disclosed in document D1 (see D1, p.434, lines 38-40 and Fig.2) are purified and cannot be distinguished from the recombinant protein as it is characterized in claim 18. The same is true for the fragments or analogs of said recombinant protein. Thus, claim 18 lacks novelty.

2.2 The subject-matter of claims 1 to 17 and 19 to 25 seems to be novel over the cited prior art.

3) Inventive activity (Article 33 (3) PCT)

3.1) Document D1 is considered to represent the most relevant state of the art. It discloses the isolation of transferrin binding proteins of *Moraxella* by methods known in the art (see D1, p.443-444, Affinity isolation experiments and D2 claim 2) and more particularly two transferrin binding proteins, Tbp1 and Tbp2, which were purified (see D1, p.434, lines 38-40 and Fig.2) and were used in direct binding assays (see D1, p.434, lines 38-40 and Fig.2).

The difference between the content of D1 and the subject-matter of the present claim 1 is that the subject-matter of claim 1 discloses the nucleic acid molecule encoding the transferrin receptor protein of *Moraxella* or a fragment or an analog thereof.

The problem to be solved by the present invention may therefore be regarded as to obtain a nucleic acid encoding the transferrin binding receptor of *Moraxella*. In order to solve the problem posed, the skilled person would have selected the purified Tbp1 and Tbp2 proteins, isolated from *Moraxella* (*Branhamella*) *catarrhalis* strain 4223, and would have applied standard molecular biology techniques to determine the corresponding nucleic acid sequence (e.g. microsequencing, PCR primers synthesis, library screening). It is standard laboratory practice to determine the N-terminal amino acid sequence of a protein using microsequencing techniques or to digest said protein and sequence the internal peptide fragments. It is again common laboratory practice to synthesize degenerated oligonucleotides corresponding to the identified amino acid sequences and to use these oligonucleotides to screen a *Moraxella* *Branhamella* *catarrhalis* strain 4223 DNA library or as an alternative to perform PCR using the same oligonucleotides and the same DNA library. Moreover, this approach is regularly used to determine the nucleic acid sequence of proteins that have already been isolated. As a consequence, the skilled person would have obtained the nucleic acids encoding both Tbp1 and Tbp2 of *Moraxella catarrhalis* strain 4223, or at least equivalents to the sequences as claimed in part a) and b) of claim 6, or at least sequences hybridizing under stringent conditions to any one of the DNA sequences defined in part a) or b) of claim 6, or being at least 90% identical to part a) or b) of claim 6.

Thus, the solution proposed in claims 1 to 7 of the present application cannot be considered as involving an inventive step.

- 3.2) In view of the paragraph 3.1 above, it would be obvious for the skilled person to contemplate the use of said nucleic acid or primers originating from *Moraxella catarrhalis* strain 4223 as a tool for isolating the sequence of *Moraxella catarrhalis* from another strain. Thus, present claim 8 cannot be considered as involving an inventive step.
- 3.3) Vectors, a method of producing protein using inclusion bodies technique, a transformed host, a transferrin receptor protein (Tbp1 or Tbp2) or fragments or analogs of said protein, ~~devoid of other proteins of the *Moraxella* strain~~, an immunogenic composition containing transferrin receptor protein and an adjuvant (see D2, claim 12), a method for generating a immune response using a

immunogenic composition (see D2, p.24-25 example 3), a method of detecting nucleic acid (hybridization) in a sample and a diagnostic kit comprising the constituents necessary for said detection are embodiments known in the art. Since the nucleic acid molecule claimed lacks an inventive step, the combination of said nucleic acid molecule with the above listed embodiments as claimed in claims 9-25, can neither be considered as involving an inventive step.

4) Clarity (Article 6 PCT)

- 4.1) The terms "fragment" and "analog" used in present claim 1, are vague and indefinite. Indeed a "fragment" can be as short as a trinucleotide and an "analog" can be any nucleotide molecule related, to what extent is open to interpretation, to the nucleotide defined in claim 1.
- 4.2) The immunogenic composition of claim 22 comprises at least one active component selected from the group consisting of (A) a purified and isolated nucleic acid molecule encoding a transferrin receptor protein ... (B) a purified and isolated nucleic acid molecule having the DNA sequence selected from the SEQ ID Nos It is not clear whether the nucleic acid molecule or the product encoded by said nucleic acid molecule leads to said immunogenicity.

5) Industrial applicability (Article 33 (4) PCT)

According to Rule 67.1(iv), the International Preliminary Examination Authority, in the present case the EPO, is not required to carry out an international preliminary examination if the subject-matter of the international application relates to methods of treatment of the human or animal body by surgery or therapy, as well as diagnostic methods. The method defined in claim 23 is a method of treatment of the human body or animal body and thus no international examination with regard to industrial applicability has been performed for this claim.

INTERNATIONAL SEARCH REPORT

In tior lication No
PCT/CH/97/00163A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K14/22 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 97 13785 A (CONNAUGHT LAB ;YANG YAN PING (CA); MYERS LISA E (CA); HARKNESS ROB) 17 April 1997 see the whole document ---	1-25
Y	WO 90 12591 A (UNIV TECHNOLOGIES INTERNATIONA ;SCHRYVERS ANTHONY BERNARD (CA)) 1 November 1990 see claims 1-26 --- -/--	1-25

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

17 July 1997

Date of mailing of the international search report

30 JULY 1997 (30.07.97)

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Nauche, S

INTERNATIONAL SEARCH REPORT

Int. Application No. [REDACTED]

PCT/C 97/00163

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MICROBIAL PATHOGENESIS, vol. 15, 1993, pages 433-445, XP000612196 RAONG-HUA YU ET AL: "THE INTERACTION BETWEEN HUMAN TRANSFERRIN AND TRANSFERRIN BINDING PROTEIN 2 FROM MORAXELLA (BRANHAMELLA) CATARRHALIS DIFFERS FROM THAT OF OTHER HUMAN PATHOGENS" see the whole document ---	1-25
A	WO 95 33049 A (PASTEUR MERIEUX SERUMS VACC ;TRANSGENE SA (FR); MILLET MARIE JOSE) 7 December 1995 see the whole document ---	1-25
A	WO 93 08283 A (UNIV SASKATCHEWAN) 29 April 1993 see the whole document -----	1-25

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA 97/00163

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 23
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 23 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

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2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. or. Publication No

PCT/CA/97/00163

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9713785 A	17-04-97	AU 7208296 A	30-04-97
WO 9012591 A	01-11-90	US 5292869 A	08-03-94
		AU 649950 B	09-06-94
		AU 5526190 A	16-11-90
		EP 0528787 A	03-03-93
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WO 9533049 A	07-12-95	FR 2720408 A	01-12-95
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		CA 2167936 A	07-12-95
		EP 0720653 A	10-07-96
		FI 960428 A	28-03-96
		HU 75992 A	28-05-97
		JP 9501059 T	04-02-97
		NO 960332 A	21-03-96
WO 9308283 A	29-04-93	US 5417971 A	23-05-95
		AU 2751392 A	21-05-93
		CA 2121364 A	29-04-93
		EP 0610260 A	17-08-94
		US 5521072 A	28-05-96